Case Report

Missed Opportunities for Intervention in a Patient With Prolonged Postoperative Delirium

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ABSTRACT

Purpose: Postoperative delirium is a common and costly state of brain dysfunction that complicates postsurgical management in some patients. The purpose of this report was to describe a case of prolonged postoperative delirium and to review the appropriate identification and management of this condition.

Methods: A 56-year-old female patient who presented with newly diagnosed diabetes mellitus and dry gangrene underwent a vascular bypass procedure while under general anesthesia. After extubation, the patient became disoriented and agitated.

Findings: The delirium continued in a hypoactive form for 10 days before it progressed to severe agitation. During the patient's 2-month hospitalization, she underwent 6 additional surgeries. Eventually, the delirium improved with the use of antipsychotic agents, and the patient was discharged to a skilled nursing facility.

Implications: This patient's history, medications, and anesthetic and surgical exposure placed her at high risk for postoperative delirium. Her exceptionally prolonged course of postoperative delirium was likely perpetuated by a multitude of factors, including the continued use of high-risk medications, the stress of repeated surgeries, urinary issues, and infection.

Conclusion: In this high-risk patient, a proactive approach to the prevention and treatment of delirium may have avoided or mitigated the prolonged delirium and, potentially, long-term cognitive deficits. (*Clin Ther*. 2015;37:2706–2710) Published by Elsevier HS Journals, Inc.

Key words: anesthesia, benzodiazepines, delirium, postoperative surgery.

INTRODUCTION

Delirium is an acute brain dysfunction characterized by dynamic levels of attention, cognition, and consciousness. It is common among elderly and/or hospitalized patients and places a significant burden on the health care system. Delirium is common in postsurgical patients, with an estimated prevalence of 10% to 80%, depending on the particular population being investigated.[1] Delirium has been associated with a number of adverse outcomes, including prolonged hospital stay and increased risks for mortality and functional decline.[2,3] The annual costs of hospitalization in delirious patients are more than twice those of nondelirious patients—US $38 to $152 billion.[4] Delirium, particularly the most common subtype, hypoactive delirium, is poorly identified despite its high prevalence among hospitalized patients.[5] Improvements in the identification and prophylaxis of delirium may both improve clinical care and reduce costs.

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Delirium may occur if a susceptible individual experiences a major stressor, such as infection or surgery.[6] General anesthesia typically involves the administration of several clinical therapeutics that might contribute to delirium, such as anticholinergic, antihistamine, benzodiazepine and/or opioid agents.[5] An elevated exposure to the anesthetic agent, as measured by processed electroencephalography (EEG), may also increase the risk for delirium.[7] Modification of the anesthetic regimen in high-risk patients may represent a strategy for reducing the risk for postoperative delirium. Herein we report an unusual case of prolonged postoperative delirium in a patient with numerous risk factors and triggers.

CASE DESCRIPTION

A 56-year-old woman with hypertension and newly diagnosed diabetes mellitus presented to the hospital with dry gangrene of the small toe. She denied the use of alcohol, tobacco, or other recreational drugs and was not on any opioid medications at the time of presentation. Her course was complicated by sepsis and acute kidney injury, so surgical management was deferred. During this period, the patient experienced a brief episode of delirium, which was attributed to treatment with gabapentin 300 mg TID and oxycodone 5 mg BID. The creatinine concentration peaked at 4 mg/dL and decreased to 2.8 mg/dL on discharge. On readmission, treatment with gabapentin at the prior dose was resumed, and the patient received oral diphenhydramine 25 mg PRN for itching and oxycodone at an average dose of 30 mg/d PRN for pain management. The patient had had an uneventful diagnostic angiogram, the preparation for which she received sedation with midazolam 2 mg and fentanyl 100 μg over 40 minutes. Her creatinine had normalized to 0.8 mg/dL. The following week, she presented for femoral to anterior tibial artery bypass while under general anesthesia.

Preoperatively, the patient had an appropriate mood and affect and consented to being a part of a prospective observational study on emergence from anesthesia. After premedication with midazolam 2 mg, she underwent induction with intravenous propofol and maintenance with inhalational sevoflurane. During the 340-minute duration anesthesia, she received fentanyl 500 μg and hydromorphone 0.4 mg. As a part of the approved research protocol, a frontal EEG from an abbreviated montage was recorded during surgery for offline analysis. Two episodes of abrupt cortical arousals were evident on the EEG as increases in high-frequency power. The first occurred early in the surgery, and the second at the conclusion of surgery. On examination of the anesthesia record, both of these cortical arousals coincided with movement by the patient, and both were treated with a bolus dose (50 mg) of propofol. Approximately 15 minutes later, the patient was extubated. On exiting the surgical suite, the patient was breathing spontaneously but not able to say her name or current location when asked.

In the recovery room, the patient became agitated and confused. At 15 minutes after emergence from anesthesia, the result of a Confusion Assessment Method for the ICU screening tool[8] was positive. The agitation was treated with an additional 4 mg of midazolam in divided doses, and the patient received two 12.5-mg doses of promethazine. She calmed eventually and could be redirected by the staff of the postanesthesia care unit. At 1 hour after emergence, the result of a second Confusion Assessment Method for the ICU screen was positive for delirium.

After a planned transfer to the ICU, the patient continued to have periods of confusion but was stable for transfer to the floor on postoperative day (POD) 2. She was still receiving diphenhydramine despite continued episodes of confusion and agitation. After a toe amputation on POD9, the patient was disoriented and repeatedly removed her dressings and picked at her wounds. On POD11, the patient was placed in restraints and started a fire in an attempt to burn them off. The psychiatry service recommended a sepsis workup as a possible cause of delirium. She was transferred back to the ICU and received haloperidol 2 mg BID for 3 days, as recommended by the psychiatry service. The sepsis workup was negative; subsequent surgeries are shown in the **Figure**. During this time, she also had persistent urinary retention requiring repeated urinary catheter placement.

On POD21, the patient was transferred from the ICU to the general surgical ward and paired 1:1 with a patient safety monitor. Her medical record listed near-daily episodes of confusion and aggression toward staff. She repeatedly removed her dressings and intravenous catheter. On POD42, the patient threatened suicide and was started on quetiapine 25 mg BID. When the patient developed difficulty swallowing the tablets, treatment was changed to risperidone elixir 0.5 mg via feeding tube. In the weeks that followed, the patient's clinical and mental statuses slowly

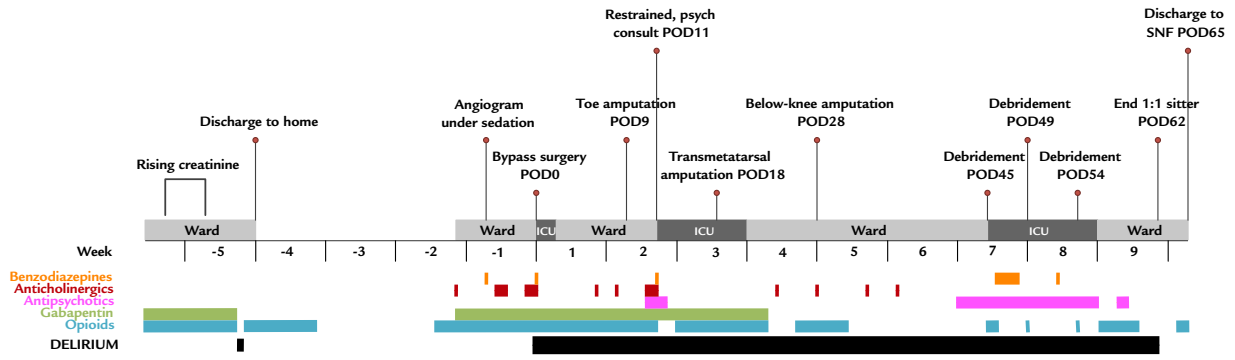

Figure. Timeline of patient's clinical course. Time 0 is the date of bypass surgery. ICU= intensive care unit; POD = postoperative day; SNF = skilled nursing facility.

improved. After several débridements and another ICU stay, the patient was discharged to a skilled nursing facility on POD65.

At a follow-up appointment on POD85, the patient was well groomed and had no evidence of delirium. She did not report any intraoperative awareness. She did report some persistent memory issues, such as not knowing how many years she had been married, and recalled an episode of delusion during her hospitalization. She graciously gave consent to have her case published with the hope that future patients may avoid some of the psychological trauma she endured.

DISCUSSION

The exceptionally protracted course of the present case illustrates the importance of identifying patients at high risk for postoperative delirium and taking a proactive approach to its prevention. The present case illustrates a variety of risk factors for delirium and a number of missed opportunities to prevent or treat it. The patient's prior episode of delirium in the setting of infection and renal failure was a clue that the patient was susceptible. During the perioperative period, several medications known to increase the risk for delirium in at-risk individuals were administered, including a benzodiazepine agent (midazolam), an antihistamine agent (diphenhydramine), and another medication with significant anticholinergic properties (promethazine).[9] Although the patient was not elderly in the conventional sense, her constellation of comorbid conditions may have placed her at increased risk.[10] Because major vascular surgery carries a high risk for delirium,[5] knowledge of the patient's prior susceptibility could have prompted some preventive measures. Nonpharmacologic and behavioral interventions could have been initiated preoperatively.[6,11] The American Geriatrics Society (AGS) guideline does not recommend medicating delirious patients who are not agitated, but instead encourages nonpharmacologic measures, such as cognitive stimulation, structured orientation, methods of maintaining sleep hygiene, mobilization, and sensory optimization.[6,12,13] Among hospitalized patients in previous studies, the implementation of these interventions—which include word games, discussion of current events, boards reflecting the names of care team members, exposure to natural light during the waking hours, and reinforcement of use of visual and hearing aids—has been associated with reductions in the prevalence of delirium of 30% to 40%.[13,14] The use of the antihistamine and the benzodiazepine should have been avoided in keeping with the recent AGS guideline and the 2012 AGS Beers criteria, a compendium of medications the use of which should be avoided in the elderly due to a risk for confusion.[6,15] The AGS guideline also recommends limiting anesthetic depth through the use of a processed EEG.

At this time, no drugs have an approved indication for delirium. Based on the known neurotransmitter imbalances in delirium, a variety of drug classes have been investigated for use in the prophylaxis or management of delirium, including antipsychotic, α_2 agonist, and acetylcholinesterase inhibitor agents.[16] The use of antipsychotic agents for prophylaxis has shown mixed

results, but a recent meta-analysis suggested benefit in high-risk individuals.[17] Haloperidol has been reported to be useful for the treatment of agitation associated with delirium, and the risk for arrhythmia resulting from the administration of a dose of haloperidol in this situation is quite low.[18,19] Ketamine[20] and dexmedetomidine[21] may also offer benefits but have not been extensively studied for use in preventing delirium. Pain management represents a dilemma because high-dose opioids may increase delirium in high-risk patients[22] but poor pain control is also a risk factor.[6] In the present case, surgery was not amenable to regional anesthesia, but the patient may have benefited from a more multimodal analgesic approach. The exposure to statins was recently suggested to reduce delirium during critical illness, potentially due to an antiinflammatory effect.[23] Melatonin agonists have also emerged as a potential therapy for delirious patients due to their effects on the sleep–wake cycle and relatively benign adverse-events profile.[24]

An analysis of neurophysiological activity while the patient was under anesthesia may provide some clues about the development of the abnormal postanesthesia trajectory. Although reflexive movement during surgery is not indicative of a patient's awareness, the acute treatment of unintended movement during surgery is important for maintaining safety. "Light" anesthesia can be managed by an increase in maintenance anesthesia dose, administration of an analgesic medication, administration of a neuromuscular blockade, or removal of the stimulus. Propofol is a way to swiftly "deepen" the anesthetic effect; it exerts its main anesthetic activity via the enhancement of inhibitory signaling through specific sites on the type A γ-aminobutyric acid receptor,[25] which is the same molecular target of benzodiazepine agents. It is possible that the bolus dosing of propofol compounded the effect of the pre- and postoperative benzodiazepine agent in this individual. This concept is supported in part by the EEG analysis, which showed a sustained cortical activation associated with the propofol dosing and failure to achieve significant power in the α band (8–14 Hz), which has been associated with successful suppression of noxious stimulation under anesthesia.[26]

CONCLUSIONS

Delirium, a state of acute organ failure akin to renal or respiratory failure, is common among surgical patients. Prolonged delirium has potentially serious consequences, such as lengthy hospital stays, psychological trauma, and the need for rehabilitation. The present patient's preceding episode of delirium highlights the importance of documenting this history on a "permanent problem list" for alerting clinicians to avoid potential triggers during care. In this case, a confluence of multiple factors, including frailty, history of delirium, use of high-risk medications, and high γ-aminobutyric acid–ergic neurophysiologic stimulation, likely contributed to the precipitation of delirium in this patient. Hypoactive delirium is more common than is agitated delirium but is easily overlooked and requires active screening and aggressive management. In elderly patients, a multimodal approach is needed for managing postoperative delirium, including the identification of high-risk patients, prophylactic measures such as nonpharmacologic interventions[13] and EEG-guided intraoperative decision making, and the judicious use of antipsychotic and other pharmacologic agents.[6,27] Consultation with a geriatric specialist might also help to optimize care in these high-risk patients. Patients and their caregivers should be appropriately educated about delirium and supported throughout its course. Together, these measures might reduce the risk for delirium and mitigate its effects when it occurs.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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